# WEST

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| DB Name | Query | Hit Count | Set Name |
|---|---|---|---|
| USPT,JPAB,EPAB,DWPI | 123 and hemophilia | 6 | L25 |
| USPT,JPAB,EPAB,DWPI | 123 and coagulation | 5 | L24 |
| DWPI,EPAB,JPAB,USPT | 11 and ((14 or 15) same factor) | 48 | L23 |
| USPT,JPAB,EPAB,DWPI | 18 and (mutant$1 or mutation$1) | 24 | L22 |
| USPT,JPAB,EPAB,DWPI | 18 same (mutant$1 or mutation$1) | 2 | L21 |
| USPT,JPAB,EPAB,DWPI | 119 and (mutant$1 or mutation$1) | 12 | L20 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) and 19 | 14 | L19 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) same 110 | 7 | L18 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) same 19 | 0 | L17 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) and 114 | 129 | L16 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) same 114 | 4 | L15 |
| USPT,JPAB,EPAB,DWPI | "factor VIII" | 3148 | L14 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) same 112 | 88 | L13 |
| USPT,JPAB,EPAB,DWPI | factor VIII | 735504 | L12 |
| USPT,JPAB,EPAB,DWPI | (14 or 15) same 16 | 4 | L11 |
| USPT,JPAB,EPAB,DWPI | (creatine adj kinase) with promoter | 34 | L10 |
| USPT,JPAB,EPAB,DWPI | (actin with promoter) with skeletal | 43 | L9 |
| USPT,JPAB,EPAB,DWPI | collagen same 16 | 37 | L8 |
| USPT,JPAB,EPAB,DWPI | intron same 16 | 31 | L7 |
| USPT,JPAB,EPAB,DWPI | "factor IX" | 1544 | L6 |
| USPT,JPAB,EPAB,DWPI | AAV same (virus or viral) | 594 | L5 |
| USPT,JPAB,EPAB,DWPI | 13 adj (virus or viral) | 1308 | L4 |
| DWPI,EPAB,JPAB,USPT | adeno-associated | 1344 | L3 |
| DWPI,EPAB,JPAB,USPT | (HIGH-KATHERINE-A OR HERZOG-ROLAND-W OR HERZOG-ROLAND)/IN | 5 | L2 |
| USPT,JPAB,EPAB,DWPI | ((514/44 )!.CCLS. (424/93.2 424/93.6 )!.CCLS. (435/320.1 )!.CCLS. (536/23.5 )!.CCLS.) | 12223 | L1 |

09/343,540

**STN search 09/393844 November 21, 2000**
**databases searches, search terms, and selected abstracts below**

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(FILE 'HOME' ENTERED AT 15:03:18 ON 21 NOV 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 15:03:34 ON 21 NOV 2000
L1 9480 S FACTOR(W)IX
L2 4238 S ADENO-ASSOCIATED
L3 2567 S AAV
L4 2406 S L3 AND (VIRUS OR VIRAL)
L5 172970 S COAGULATION
L6 214414 S COLLAGEN
L7 3596 S COLLAGEN(W)IV
L8 64931 S INTRON
L9 1087 S (INVERTED(W)TERMINAL)(W)REPEAT?
L10 277846 S PROMOTER?
L11 360 S HIGH K?/AU
L12 453 S HERZOG R?/AU
L13 40 S (L11 OR L12) AND (L2 OR L4)
**L14** 27 DUP REM L13 (13 DUPLICATES REMOVED)
L15 105 S L1 AND (L2 OR L4)
**L16** 1 S L15 AND L8
L17 53 S L15 AND PY<1999
**L18** 42 DUP REM L17 (11 DUPLICATES REMOVED)
**L19** 1 S L18 AND L7
L20 4 S L18 AND L6
L21 853974 S MUTANT OR MUTATION?
**L22** 6 S L1 AND L21 AND L7
L23 40 S (L2 OR L4) AND INTRON?
**L24** 26 DUP REM L23 (14 DUPLICATES REMOVED)
L25 4 S L24 AND L9
L26 27 S (L2 OR L4) AND L5 AND MUSCLE
**L27** 17 DUP REM L26 (10 DUPLICATES REMOVED)
**L28 89 S L14 OR L16 OR L18 OR L19 OR L20 OR L22 OR L24 OR L27**
**L29 85 DUP REM L28 (4 DUPLICATES REMOVED)**
**L30 61 S L29 AND PY<1999**

L30 ANSWER 2 OF 61 MEDLINE
ACCESSION NUMBER: 1998197326 MEDLINE
DOCUMENT NUMBER: 98197326

TITLE: Direct intramuscular injection with recombinant **AAV** vectors results in sustained expression in a dog model of hemophilia.
AUTHOR: Monahan P E; Samulski R J; Tazelaar J; Xiao X; Nichols T C; Bellinger D A; Read M S; Walsh C E
CORPORATE SOURCE: UNC Gene Therapy Center, University of North Carolina, Chapel Hill 27599, USA.
CONTRACT NUMBER: DK09550-02 (NIDDK)
HL 48347 (NHLBI)
SOURCE: GENE THERAPY, **(1998 Jan)** 5 (1) 40-9.
Journal code: CCE. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
AB A recombinant **adeno-associated virus** (rAAV) vector carrying the human **factor IX** cDNA was tested for safety and therapeutic gene expression in a canine model of human hemophilia B. Intramuscular delivery of rAAV was chosen based on our previous work which described long-term (> 1.5 years) reporter gene expression in immunocompetent mice following direct **muscle** injection. For the current study, rAAV with the human **factor IX** (hF.IX) cDNA under the control of the cytomegalovirus (CMV) immediate-early promoter was constructed, and rAAV/hF.IX proved capable of transducing hemophilic dog primary fibroblast cultures in a dose-dependent fashion. Direct intramuscular injection of 2.5 x 10(12) rAAV/hF.IX **virus** particles into the hindlimbs of a hemophilia B dog was tolerated without bleeding or systemic reaction, and the animal was asymptomatic throughout the entire study. Transient reduction in the whole blood clotting time (WBCT) occurred during the first week, with the anticipated development of an antihuman F.IX inhibitor antibody which corresponded with the loss of **coagulation** correction. At 10 weeks after vector administration, immunohistochemical analysis of injected **muscle** confirmed continued hF.IX expression. Limited areas of focal lymphocytic infiltration and myofiber pathology were detected which directly correlated with positive antibody staining for helper adenovirus contamination. PCR tissue analysis revealed rAAV/hF.IX DNA solely in injected **muscle** tissue and adjacent lymph node, without dissemination to other organs (including gonads). This first large animal study suggests that intramuscular gene delivery using rAAV vectors is safe and supports continued development of this approach for gene therapy of human diseases, including hemophilia B.

L30 ANSWER 3 OF 61 MEDLINE
ACCESSION NUMBER: 1998056844 MEDLINE

DOCUMENT NUMBER: 98056844
TITLE: Gene therapy for the hemophilias.
AUTHOR: Walter J; **High K A**
CORPORATE SOURCE: Department of Cardiothoracic Surgery, University of Vienna, Austria.
SOURCE: ADVANCES IN VETERINARY MEDICINE, **(1997)** 40 119-34. Ref: 48
Journal code: CV2. ISSN: 1093-975X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
AB There are many lines of evidence that suggest the eventual success of gene therapy as a treatment strategy for hemophilia. Because current treatment protocols using plasma-derived or recombinant proteins are far from ideal, the safe and efficient substitution of the defective gene by a normal copy of the gene, or at least its addition, would be of great benefit to the patient and may even be a potential cure. However, the construction of efficient gene therapy vehicles has proven quite difficult in the past and, so far, there is no system that promises to have all the desired features without any serious disadvantages. In general, either the levels of transgene expression are too low (because of the low titers achieved during the generation of the **virus**) or shortlived (e.g., because of the specific shut-off of the transferred promoter) as is often seen with retroviruses, or in the case of adenoviral vectors, expression is limited because of a strong immune response of the host. Clearly, much work remains to be done to optimize these promising though still imperfect vector systems. In the case of adenovirus, the development of less immunogenic vectors or in vivo modulation of the host immune system may hold promise for improvements. Reports by Yang et al. (1995) and Kay et al. (1995) are promising steps in the direction of immunomodulation. Both attenuate the immune reaction to the adenoviral vector by simultaneous application of either an interleukin or an immunoglobulin, respectively. When IL-2 was administered, the amounts of IgA were reduced and successful administration of a second dose of **virus** was possible. When CTLA4-Ig, an immunoglobulin that blocks the second signal during antigen presentation, was administered, a markedly prolonged expression of the transgene resulted. In vivo trials with **AAV** vectors have been carried out for some diseases (Flotte et al., 1993; Kaplitt et al., 1994) but not for hemophilia. Advances in high-titer **AAV** vector preparation will make this approach more feasible. The pace continues to quicken in the development of nonviral modes of gene delivery (Perales et al., 1994). Although these results are encouraging for the future of gene therapy as a treatment for genetic diseases, much work remains to be done to make this potential alternative a reality for treatment of hemophilia.

L30 ANSWER 4 OF 61 MEDLINE
ACCESSION NUMBER: 97448273 MEDLINE
DOCUMENT NUMBER: 97448273
TITLE: Recombinant **adeno-associated** virus delivers human **factor IX** in mice [news].
AUTHOR: Stewart A
SOURCE: MOLECULAR MEDICINE TODAY, **(1997 Sep)** 3 (9) 368.
Journal code: CMK. ISSN: 1357-4310.
PUB. COUNTRY: ENGLAND: United Kingdom
News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803

L30 ANSWER 5 OF 61 MEDLINE
ACCESSION NUMBER: 97351511 MEDLINE
DOCUMENT NUMBER: 97351511
TITLE: Persistent and therapeutic concentrations of human **factor IX** in mice after hepatic gene transfer of recombinant **AAV** vectors.
AUTHOR: Snyder R O; Miao C H; Patijn G A; Spratt S K; Danos O; Nagy D; Gown A M; Winther B; Meuse L; Cohen L K; Thompson A R; Kay M A
CORPORATE SOURCE: Somatix Therapy Corporation, Alameda, California 94501, USA.
CONTRACT NUMBER: HL53682 (NHLBI)
DK47754 (NIDDK)
SOURCE: NATURE GENETICS, **(1997 Jul)** 16 (3) 270-6.
Journal code: BRO. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
AB Haemophilia B, or **factor IX** deficiency, is a X-linked recessive disorder that occurs in about one in 25,000 males, and severely affected people are at risk for spontaneous bleeding into numerous organs. Bleeding can be life-threatening or lead to chronic disabilities with haemophilic arthropathy. The severity of the bleeding tendency varies among patients and is related to the concentration of functional plasma **factor IX**. Patients with 5-30% of the normal **factor IX** have mild haemophilia that may not be

recognized until adulthood or after heavy trauma or surgery. Therapy for acute bleeding consists of the transfusion of clotting-factor concentrates prepared from human blood and recombinant clotting factors that are currently in clinical trials. Both recombinant retroviral and adenoviral vectors have successfully transferred **factor IX** cDNA into the livers of dogs with haemophilia B. Recombinant retroviral-mediated gene transfer results in persistent yet subtherapeutic concentrations of **factor IX** and requires the stimulation of hepatocyte replication before vector administration. Recombinant adenoviral vectors can temporarily cure the coagulation defect in the canine haemophilia B model; however, an immune response directed against **viral** gene products made by the vector results in toxicity and limited gene expression. The use of recombinant **adeno-associated virus** (rAAV) vectors is promising because the vector contains no **viral** genes and can transduce non-dividing cells. The efficacy of in vivo transduction of non-dividing cells has been demonstrated in a wide variety of tissues. In this report, we describe the successful transduction of the liver in vivo using r-**AAV** vectors delivered as a single administration to mice and demonstrate that persistent, curative concentrations of functional human **factor IX** can be achieved using wild-type-free and adenovirus-free rAAV vectors. This demonstrates the potential of treating haemophilia B by gene therapy at the natural site of **factor IX** production.

L30 ANSWER 6 OF 61 MEDLINE
ACCESSION NUMBER: 97303212 MEDLINE
DOCUMENT NUMBER: 97303212
TITLE: Stable gene transfer and expression of human blood **coagulation factor IX** after intramuscular injection of recombinant **adeno-associated virus**.
AUTHOR: **Herzog R W**; Hagstrom J N; Kung S H; Tai S J; Wilson J M; Fisher K J; **High K A**
CORPORATE SOURCE: Department of Pediatrics, University of Pennsylvania School of Medicine, and The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.
CONTRACT NUMBER: R01 HL53668 (NHLBI)
P50 HL54500 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 May 27)** 94 (11) 5804-9.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970803
AB We sought to determine whether intramuscular injection of a recombinant **adeno-associated virus** (rAAV) vector expressing human **factor IX** (hF.IX) could direct expression of therapeutic levels of the transgene in experimental animals. High titer (10(12)-10(13) vector genomes/ml) rAAV expressing hF.IX was prepared, purified, and injected into hindlimb **muscles** of C57BL/6 mice and Rag 1 mice. In the immunocompetent C57BL/6 mice, immunofluorescence staining of **muscle** harvested 3 months after injection demonstrated the presence of hF.IX protein, and PCR analysis of **muscle** DNA was positive for **AAV** DNA, but no hF.IX was detected in mouse plasma. Further studies showed that these mice had developed circulating antibodies to hF.IX. In follow-up experiments in Rag 1 mice, which carry a **mutation** in the recombinase activating gene-1 and thus lack functional B and T cells, similar results were seen on DNA analysis of **muscle**, but these mice also demonstrated therapeutic levels (200-350 ng/ml) of F. IX in the plasma. The time course of F.IX expression demonstrates that levels gradually increase over a period of several weeks before reaching a plateau that is stable 6 months after injection. In other experiments we demonstrate colocalization of hF.IX and **collagen IV** in intersitial spaces between **muscle** fibers. **Collagen IV** has recently been identified as a F.IX-binding protein; this finding explains the unusual pattern of immunofluorescent staining for F.IX shown in these experiments. Thus rAAV can be used to direct stable expression of therapeutic levels of F.IX after intramuscular injection and is a feasible strategy for treatment of patients with hemophilia B.

L30 ANSWER 7 OF 61 MEDLINE
ACCESSION NUMBER: 97208916 MEDLINE
DOCUMENT NUMBER: 97208916
TITLE: Recombinant **adeno-associated virus** for muscle directed gene therapy.
AUTHOR: Fisher K J; Jooss K; Alston J; Yang Y; Haecker S E; **High K**; Pathak R; Raper S E, Wilson J M
CORPORATE SOURCE: Institute for Human Gene Therapy, University of Pennsylvania Health System, Philadelphia 19104, USA.
SOURCE: NATURE MEDICINE, **(1997 Mar)** 3 (3) 306-12.
Journal code: CG5. ISSN: 1078-8956.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706
ENTRY WEEK: 19970601
AB Although gene transfer with **adeno-associated virus** (**AAV**) vectors has typically been low, transduction can be enhanced in the presence of adenovirus gene products through the formation of double stranded, non-integrated **AAV** genomes. We describe the unexpected finding of high level and stable transgene expression in mice following intramuscular injection of purified recombinant **AAV** (rAAV). The rAAV genome is efficiently incorporated into nuclei of differentiated muscle fibers where it persists as head-to-tail concatamers. Fluorescent in situ hybridization of muscle tissue suggests single integration sites. Neutralizing antibody against **AAV** capsid proteins does not prevent readministration of vector. Remarkably, no humoral or cellular immune responses are elicited to the neoantigenic transgene product E. coli beta-galactosidase. The favorable biology of rAAV in muscle-directed gene therapy described in this study expands the potential of this vector for the treatment of inherited and acquired diseases.

L30 ANSWER 8 OF 61 MEDLINE
ACCESSION NUMBER: 97188484 MEDLINE
DOCUMENT NUMBER: 97188484
TITLE: Persistent expression of human clotting **factor IX** from mouse liver after intravenous injection of **adeno-associated virus** vectors.
AUTHOR: Koeberl D D; Alexander I E; Halbert C L; Russell D W; Miller A D
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
CONTRACT NUMBER: HL41212 (NHLBI)
DK47754 (NIDDK)
HL03100 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Feb 18)** 94 (4) 1426-31.
Journal code: PV3. ISSN: 0027-8424.
PUB COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970505
AB We previously found that gene transduction by **adeno-associated virus** (**AAV**) vectors in cell culture can be stimulated over 100-fold by treatment of the target cells with agents that affect DNA metabolism, such as irradiation or topoisomerase inhibitors. Here we show that previous gamma-irradiation increased the transduction rate in mouse liver by up to 900-fold, and the topoisomerase inhibitor etoposide increased transduction by about 20-fold. Similar rates of hepatic transduction were obtained by direct injection of the liver or by systemic delivery via tail vein injection. Hepatocytes were much more efficiently transduced than other cells after systemic delivery, and up to 3% of all hepatocytes could be transduced after one vector injection. The presence of wild-type **AAV**, which contaminates many **AAV** vector preparations, was required to observe a full response to gamma-irradiation. Injection of mice with **AAV** vectors encoding human clotting **factor IX** after gamma-irradiation resulted in synthesis of low levels of human clotting **factor IX** for the 5-month period of observation. These studies show the potential of targeted gene transduction of the liver by **AAV** vectors for treatment of various hematological or metabolic diseases.

L30 ANSWER 9 OF 61 MEDLINE
ACCESSION NUMBER: 97169874 MEDLINE
DOCUMENT NUMBER: 97169874
TITLE: Comparison of retroviral and **adeno-associated viral** vectors designed to express human clotting **factor IX**.
AUTHOR: Chen L; Perlick H; Morgan R A
CORPORATE SOURCE: Gene Transfer Technology Section, National Center for Human Genome Research, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: HUMAN GENE THERAPY, **(1997 Jan 20)** 8 (2) 125-35.
Journal code: A12. ISSN: 1043-0342.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970801
AB Several different designs for retroviral and **adeno-associated virus** (**AAV**) vectors were developed to express human clotting **factor IX**. Seven separate retroviral vectors were constructed, including chimeric long terminal repeat (LTR)-based designs, vectors containing splice donor/acceptor sites with internal ribosome entry sites (IRES), and vectors with an internal cytomegalovirus (CMV)- or hepatitis B **virus** (HBV)-derived promoter. Five **AAV** vectors were produced using the same cassette design where a **viral** promoter was used to transcribe a

bicistronic mRNA containing **factor IX** and an IRES/neo gene. In the human hepatocyte cell line HepG2, the constructs were tested for **factor IX** production by ELISA, Northern blot, and Western blot, and for biological activity by normalization of the prolonged activated partial thromboplastin time (APTT) of **factor IX**-deficient plasma. All of the constructs produced biologically active **factor IX** in the range of 0.23-152 ng/24 hr per 10(6) cells (the HBV-promoted **factor IX AAV** vector was the least effective, and the CMV-promoted retroviral vector was the most active). Primary fibroblasts of both human and rabbit origin were also evaluated for **factor IX** production following transduction with **viral** vectors. Fibroblasts produced substantially more **factor IX** than the HepG2 cell line, with the best **AAV** vector synthesizing > 250 ng/24 hr per 10(6) cells and the best retroviral vector making > 900 ng/24 hr per 10(6) cells. Generally, we observed lower transduction efficiency and poorer expression with the **AAV** vectors versus retroviral vectors in these cell types.

L30 ANSWER 10 OF 61 MEDLINE
ACCESSION NUMBER: 97008134 MEDLINE
DOCUMENT NUMBER: 97008134
TITLE: Identification of the endothelial cell binding site for **factor IX**.
AUTHOR: Cheung W F; van den Born J; Kuhn K; Kjellen L; Hudson B G; Stafford D W
CORPORATE SOURCE: Department of Medical and Physiological Chemistry, University of Uppsala, Sweden.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1996 Oct 1)** 93 (20) 11068-73.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199701
ENTRY WEEK: 19970104
AB We previously demonstrated that the primary region of **factor IX** and IXa responsible for saturable specific binding to bovine aortic endothelial cells resides in residues 3-11 at the amino terminus of **factor IX**. We also demonstrated that **mutations** of lysine to alanine at residue 5, **factor IX** K5A, or valine to lysine at residue 10, **factor IX** V10K, resulted in a molecule unable to bind to endothelial cells. Moreover, a **mutation** with lysine to arginine at residue 5, **factor IX** K5R, resulted in a **factor IX** molecule with increased affinity for the endothelial cell binding site. In this paper we report that **collagen IV** is a strong candidate for the **factor IX** binding site on endothelial cells. **Factor IX** and **factor IX** K5R compete with 125I-labeled **factor IX** for binding to tetrameric **collagen IV** immobilized on microtiter plates, while factor X, factor VII, and **factor IX** K5A or V10K fail to compete. The Kd for wild-type **factor IX** binding to **collagen IV** in the presence of heparin was 6.8 +/- 2 nM, and the Kd for **factor IX** K5R was 1.1 +/- 0.2 nM, which agrees well with our previously published Kd values of 7.4 and 2.4 nM for binding of the same proteins to endothelial cells. Our working assumption is that we have identified the endothelial cell binding site and that it is **collagen IV**. Its physiological relevance remains to be determined.

L30 ANSWER 11 OF 61 MEDLINE
ACCESSION NUMBER: 95024009 MEDLINE
DOCUMENT NUMBER: 95024009
TITLE: Recombinant **adeno-associated virus** (rAAV)-mediated expression of a human gamma-globin gene in human progenitor-derived erythroid cells [published erratum appears in Proc Natl Acad Sci U S A 1995 Jan 17;92(2):646].
AUTHOR: Miller J L; Donahue R E; Sellers S E; Samulski R J; Young N S; Nienhuis A W
CORPORATE SOURCE: National Heart, Lung and Blood Institute, Bethesda, MD 20892.
CONTRACT NUMBER: HL 48347-03 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1994 Oct 11)** 91 (21) 10183-7.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Cancer Journals; Priority Journals
ENTRY MONTH: 199501
AB Effective gene therapy for the severe hemoglobin (Hb) disorders, sickle-cell anemia and thalassemia, will require an efficient method to transfer, integrate, and express a globin gene in primary erythroid cells. To evaluate recombinant **adeno-associated virus** (rAAV) for this purpose, we constructed a rAAV vector encoding a human

gamma-globin gene (pJM24/vHS432A gamma). Its 4725-nucleotide genome consists of two 180-bp **AAV** inverted terminal repeats flanking the core elements of hypersensitive sites 2, 3, and 4 from the locus control region of the beta-globin gene cluster, linked to a mutationally marked A gamma-globin gene (A gamma) containing native promoter and RNA processing signals. CD34+ human hematopoietic cells were exposed to rAAV particles at a multiplicity of infection of 500-1000 and cultured in semisolid medium containing several cytokines. A reverse transcriptase polymerase chain reaction assay distinguished mRNA signals derived from transduced and endogenous human gamma-globin genes. Twenty to 40% of human erythroid burst-forming unit-derived colonies expressed the rAAV-transduced A gamma-globin gene at levels 4-71% that of the endogenous gamma-globin genes. The HbF content of pooled control colonies was 26%, whereas HbF was 40% of the total in pooled colonies derived from rAAV transduced progenitors. These data establish that rAAV containing elements from the locus control region linked to a gamma-globin gene are capable of transferring and expressing that gene in primary human hematopoietic cells resulting in a substantial increase in HbF content.

L30 ANSWER 12 OF 61 MEDLINE
ACCESSION NUMBER: 93018827 MEDLINE
DOCUMENT NUMBER: 93018827
TITLE: Definition of interferon gamma-response elements in a novel human Fc gamma receptor gene (Fc gamma RIb) and characterization of the gene structure.
AUTHOR: Benech P D; Sastry K; Iyer R R; Eichbaum Q G; Raveh D P; Ezekowitz R A
CORPORATE SOURCE: Division of Hematology/Oncology, Children's Hospital, Boston, Massachusetts.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1992 Oct 1)** 176 (4) 1115-23.
Journal code: I2V. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-S45704; GENBANK-S45705; GENBANK-S45707; GENBANK-S45708; GENBANK-S45709; GENBANK-S45710; GENBANK-S75517; GENBANK-X63232; GENBANK-X63233; GENBANK-S40279
ENTRY MONTH: 199301
AB The human Fc gamma RI (CD64) is a high affinity receptor for the Fc portion of immunoglobulin (Ig), and its constitutively low expression on the cell surface of monocyte/macrophage and neutrophils is selectively upregulated by interferon gamma (IFN-gamma) treatment (Perussia, B., E. T. Dayton, R. Lazarus, V. Fanning, and G. Trinchieri. 1983. J. Exp. Med. 158:1092). Three distinct cDNAs have been cloned and code for proteins that predict three extracellular Ig-like domains (Allen, J.M., and B. Seed. 1989. Science [Wash. DC]. 243:378). Several differences in the coding region of these cDNAs suggest that in addition to polymorphic differences a second Fc gamma RI gene could possibly exist. This alternative Fc gamma RI gene (Fc gamma RIb) was defined by the lack of a genomic HindIII restriction site (van der Winkel, J. G. J., L. U. Ernst, C. L. Anderson, and I. M. Chiu. 1991. J. Biol. Chem. 266:13449). We describe the characterization a second gene (Fc gamma RIb) that has a termination codon in the third extracellular domain and therefore predicts a soluble form of a termination codon in the third extracellular domain and therefore predicts a soluble form of the receptor. We also define two distinct IFN-gamma-responsive regions in the 5' flanking sequence of Fc gamma RIb that resemble motifs that have been defined in the class II major histocompatibility complex promoter. The Fc gamma RIb promoter does not possess canonical TATA or CCAAT boxes, but does possess a palindromic motif that closely resembles the initiator sequence identified in the terminal deoxynucleotidyl transferase/human leukocyte IFN/**adeno-associated** virus type II P5 gene promoters (Smale, S. T., and D. Baltimore. 1989. Cell. 57:103; Seto, E., Y. Shi, and T. Shenk. 1991. Nature [Lond.]. 354:241; Roy, A. L., M. Meisterernst, P. Pognonec, and R. C. Roeder. 1991. Nature [Lond.]. 354:245) virus type II P5 gene promoters raising interesting questions as to its role in the basal and myeloid-specific transcription of this gene.

L30 ANSWER 13 OF 61 MEDLINE
ACCESSION NUMBER: 92348451 MEDLINE
DOCUMENT NUMBER: 92348451
TITLE: Chromosomal localization and organization of the murine genes encoding the beta subunits (AIC2A and AIC2B) of the interleukin 3, granulocyte/macrophage colony-stimulating factor, and interleukin 5 receptors.
AUTHOR: Gorman D M; Itoh N; Jenkins N A; Gilbert D J; Copeland N G; Miyajima A
CORPORATE SOURCE: Department of Molecular Biology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California 94304.
CONTRACT NUMBER: NO1-CO-74101 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1992 Aug 5)** 267 (22) 15842-8.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals

OTHER SOURCE: GENBANK-M93429; GENBANK-M93722; GENBANK-M94136;
GENBANK-M94137; GENBANK-M94138; GENBANK-M94139;
GENBANK-M94140; GENBANK-M94141; GENBANK-M94142;
GENBANK-M94143; GENBANK-M94144; GENBANK-M94145;
GENBANK-M94146; GENBANK-M94147; GENBANK-M94148;
GENBANK-M95501; GENBANK-M95502; GENBANK-M95503;
GENBANK-M95504; GENBANK-M95505; GENBANK-M95506;
GENBANK-M95507; GENBANK-M95508; GENBANK-M95509;
GENBANK-M95510; GENBANK-M95511; GENBANK-M95512;
GENBANK-M95513; +
ENTRY MONTH: 199211
AB Chromosomal genes for two mouse homologous beta subunits (AIC2A and AIC2B)
of the interleukin-3, granulocyte/macrophage colony-stimulating factor, and interleukin-5 receptors were characterized. Both AIC2A and AIC2B genes were present on a 250-kilobase MluI restriction fragment and were mapped on murine chromosome 15 (these loci were provisionally designated as Il3rb-1 (AIC2A) and Il3rb-2 (AIC2B)), closely linked to the c-sis locus. Both genes consist of 14 exons and span about 28 kb each. The major transcription initiation sites of both genes were mapped at 194 bp from the initiation codon. These genes are 95% identical up to 700 bp from the transcription initiation sites. Potential recognition sequences for hemopoietic transcription factors including GATA-1 and PU.1 in addition to a TATA-like sequence are present in the 5'-flanking region. A stretch of 20 bp including the initiation site is homologous to the corresponding region of the erythropoietin receptor and the interleukin-7 receptor genes and to the initiator sequence of the **adeno-associated** virus P5 promoter, suggesting a possible role in transcription initiation. Comparison of the exon/**intron** boundaries of AIC2A and AIC2B genes with those of other members of the cytokine receptor superfamily reveals a conserved evolutionary structure. Isolation of various forms of AIC2 cDNAs reveals differential splicing of the transcripts.

L30 ANSWER 14 OF 61 MEDLINE
ACCESSION NUMBER: 88275042 MEDLINE
DOCUMENT NUMBER: 88275042
TITLE: Synthesis of **adeno-associated** **virus** structural proteins requires both alternative mRNA splicing and alternative initiations from a single transcript.
AUTHOR: Becerra S P; Koczot F; Fabisch P; Rose J A
CORPORATE SOURCE: Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892.
SOURCE: JOURNAL OF VIROLOGY, **(1988 Aug)** 62 (8) 2745-54.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198810
AB The three **adeno-associated virus** type 2 (AAV2) structural proteins (A, B, and C) are specified by transcripts generated from the most-rightward promoter (p40). Protein C (60 kilodaltons [kDa]), the most abundantly produced, is entirely contained within B (72 kDa) which, in turn, is contained within A (90 kDa). Although neither of the known structures of p40 transcripts, an unspliced 2.6-kilobase (kb) RNA and a spliced 2.3-kb RNA, possesses an AUG-initiated open reading frame that accounts for the synthesis of proteins A and B, recent evidence indicates that B is initiated by a unique eucaryotic initiation codon (ACG) (S.P. Becerra, J.A. Rose, M. Hardy, B. Baroudy, and C.W. Anderson, Proc. Natl. Acad. Sci. USA 82:7919-7923, 1985). In the present study, we analyzed the in vitro translation of **AAV** capsid proteins from synthetic transcripts and the in vivo expression of **AAV** mRNA and capsid proteins in 293 cells transfected with **AAV** DNA constructs. The results demonstrated that **AAV** transcripts contain only one functional 5' splice donor site, that synthesis of capsid proteins from the unspliced 2.6-kb transcript is very inefficient, that transcripts without the intervening sequence (IVS) (i.e., the 2.3-kb RNA) do not produce protein A but effectively synthesize proteins B and C, and that protein A is actively synthesized from transcripts which contain the last 34 bases of the IVS. Protein A initiates within this 34-base segment in reading frame 1, apparently with the AUG codon at nucleotide 2203, and then elongates into the B and C open reading frame. Because A is inefficiently synthesized from the 2.6-kb transcript, we conclude that an effective A transcript is generated by alternative splicing and that the alternative 3' acceptor site may lie at nucleotide 2200 within a context of...CAG]GTA. The levels of B and C produced by a synthetic transcript devoid of the IVS suggest that the known 2.3-kb RNA is the main source of these proteins and indicate that this single RNA species expresses both proteins by alternative use of their respective initiation codons.

L30 ANSWER 15 OF 61 MEDLINE
ACCESSION NUMBER: 87321122 MEDLINE
DOCUMENT NUMBER: 87321122
TITLE: Gene expression in **adeno-associated** **virus** vectors: the effects of chimeric mRNA structure, helper **virus**, and adenovirus VA1 RNA.
AUTHOR: West M H; Trempe J P; Tratschin J D; Carter B J
SOURCE: VIROLOGY, **(1987 Sep)** 160 (1) 38-47.
Journal code: XEA. ISSN: 0042-6822.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198712
AB We used a recombinant plasmid containing an **adeno-associated virus** (**AAV**) genome to construct several vectors which express the gene for chloramphenicol acetyltransferase (CAT). We transfected four different **AAV**-CAT vectors into human 293 (adenovirus-transformed) cells and analyzed CAT activity We show that, for vectors using the **AAV** p40 and p19 promoter, the chimeric **AAV**-CAT transcripts began from the correct 5' position but the basal level of CAT expression depended in part on the structure of the transcript. We also examined the effects of coinfection of the cells with the helper adenovirus or cotransfection with a plasmid which expressed the adenovirus translational control RNA, VA1 RNA. Cotransfection with plasmids containing the gene for VA1 RNA resulted in elevated levels of CAT activity. VA1 RNA stimulated translation of the chimeric mRNA. However, in two cases, the VA1 RNA apparently decreased the level of mRNA. These results suggest that in addition to its function in translation, VA1 RNA acts at a second site to alter cytoplasmic accumulation of some mRNAs. Infection with adenovirus increased CAT activity several-fold by increasing the cytoplasmic levels of the chimeric **AAV**-CAT transcript. When the CAT gene is inserted down stream of the **AAV intron**, adenovirus and not VA1 RNA alone increased CAT activity by promoting accumulation of a spliced transcript.

L30 ANSWER 23 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:100400 BIOSIS
DOCUMENT NUMBER: PREV199900100400
TITLE: Gene therapy for hemophilia.
AUTHOR(S) **High, Katherine A. (1)**
CORPORATE SOURCE: (1) Child. Hosp. Philadelphia, Abramson Res. Cent., Philadelphia, PA 19104 USA
SOURCE: Quesenberry, P. J. [Editor]; Stein, G. S. [Editor]; Forget, B. G. [Editor]; Weissman, S. M. [Editor]. (1998) pp. 385-410. Stem cell biology and gene therapy. Publisher: John Wiley and Sons Ltd. Baffin Lane, Chichester PO 19 1UD, England. ISBN: 0-471-14656-0.
DOCUMENT TYPE: Book
LANGUAGE: English

L30 ANSWER 26 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:384830 BIOSIS
DOCUMENT NUMBER: PREV199800384830
TITLE: **AAV**-mediated gene transfer in dogs with hemophilia B.
AUTHOR(S): **Herzog, R. W. (1)**; Yang, E. Y.; Couto, L. B.; Hagstrom, J. N.; Elwell, D.; Chu, K.; Kung, S.-H.; Tai, S. J.; McQuiston, S. A.; Colosi, P.; Podsakoff, G. M.; Read, M. S.; Bellinger, D. A.; Brinkhous, K. M.; Nichols, T.; Kurtzman, G. J.; **High, K. A.**
CORPORATE SOURCE: (1) Dep. Pathol., Univ. Pennsylvania, Children's Hosp. Philadelphia, Philadelphia, PA USA
SOURCE: Journal of Investigative Medicine, (**March, 1998**) Vol. 46, No. 3, pp. 215A. Meeting Info.: Annual Meeting of the Association of American Physicians, American Society for Clinical Investigation, American Federation for Medical Research 1998 Biomedicine: Medical Research from Bench to Bedside Washington, D.C., USA May 1-3, 1998 American Federation for Medical Research . ISSN: 1081-5589.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 27 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:67366 BIOSIS
DOCUMENT NUMBER: PREV199800067366
TITLE: Absence of antibodies against **factor IX** following IM injection of an **AAV** vector encoding a species-specific transgene.
AUTHOR(S): **Herzog, R. (1)**; Hagstrom, J.; Kung, S.; Yang, E.; Couto, L.; Kurtzman, G.; McQuiston, S.; Colosi, P.; Elwell, D.; Nichols, T.; Belliger, D.; Read, M.; Brinkhous, K.; Tai, S.; **High, K.**
CORPORATE SOURCE: (1) Child. Hosp. Phila., Philadelphia, PA USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 240A-241A. Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 28 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:67365 BIOSIS
DOCUMENT NUMBER: PREV199800067365
TITLE: Sustained expression of human **factor IX** in a hemophilic canine following direct intramuscular injection of an **adeno-associated virus** (**AAV**) vector.
AUTHOR(S): Monahan, P. E. (1); Tazelaar, J.; Xiao, X.; Nichols, T. C.; Bellinger, D. A.; Read, M. S.; Samulski, R. J.; Walsh, C. E.
CORPORATE SOURCE: (1) Gene Therapy Cent., Univ. N.C., Chapel Hill, NC USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 240A.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 29 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:67364 BIOSIS
DOCUMENT NUMBER: PREV199800067364
TITLE: Persistent expression to human **coagulation Factor IX** following administration of **AAV** vectors to mouse **muscle** and liver.
AUTHOR(S): Nakai, H. (1); **Herzog, R.**; Iwaki, Y.; Colosi, P.; Eisensmith, R.; **High, K.**; Kurtzman, G.; Couto, L.
CORPORATE SOURCE: (1) Avigen Inc., Alameda, CA USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 240A.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 30 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:62456 BIOSIS
DOCUMENT NUMBER: PREV199800062456
TITLE: Effect of anti-retroviral drugs on efficiency of transduction and expression by a recombinant **AAV** vector expressing human **factor IX**.
AUTHOR(S): Swanson, Chad M. (1); **Herzog, Roland W.**; Kurtzman, Gary; **High, Katherine A.**
CORPORATE SOURCE: (1) Univ. Pa. Sch. Med., Children's Hosp., Philadelphia, PA 19104 USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 2, pp. 418B.
Meeting Info.: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 31 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:523194 BIOSIS
DOCUMENT NUMBER: PREV199799822397
TITLE: Gene therapy for the hemophilias.
AUTHOR(S): Walter, Johannes (1); **High, Katherine A.**
CORPORATE SOURCE: (1) Dep. Cardiothoracic Surgery, Univ. Vienna, Vienna Austria
SOURCE: Dodds, W. J. [Editor]; Womack, J. E. [Editor]. Advances in Veterinary Medicine, (1997) No. 40, pp. 119-134. Advances in Veterinary Medicine; Molecular genetics, gene transfer, and therapy.
Publisher: Academic Press, Inc. 1250 Sixth Ave., San Diego, California 92101. USA.
ISSN: 0931-4229. ISBN: 0-12-039241-0.
DOCUMENT TYPE: Book, General Review
LANGUAGE: English

L30 ANSWER 32 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:241624 BIOSIS
DOCUMENT NUMBER: PREV199799540827
TITLE: Sustained production of therapeutic levels of **factor IX** in mice following intramuscular injection of a recombinant **AAV** vector.
AUTHOR(S): **Herzog, R.**; Kung, J.; Tai, S. J.; Fisher, K.; **High, K. A.**
CORPORATE SOURCE: Dep. Pediatrics, Inst. Human Gene Therapy, Univ Pennsylvania, Children's Hosp. Philadelphia, Philadelphia, PA USA
SOURCE: Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 265A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research: Biomedicine '97 Medical Research from Bench to Bedside Washington, D.C., USA April 25-27, 1997
ISSN: 1081-5589.

DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 33 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:54069 BIOSIS
DOCUMENT NUMBER: PREV199799353272
TITLE: In vivo expression of therapeutic levels of human F.IX using a recombinant **adeno-associated viral** (**AAV**) vector.
AUTHOR(S): Kung, James (1); Hagstrom, Nathan; Walter, Johannes; Fisher, Kris; **High, Katherine A.**
CORPORATE SOURCE: (1) Univ. Pennsylvania Sch. Med., Philadelphia, PA USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 273A.
Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 34 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:53531 BIOSIS
DOCUMENT NUMBER: PREV199799352734
TITLE: Stable production in vitro of human coagulation **factor IX** expressed from **adeno-associated** virus.
AUTHOR(S): Wiener, S. M.; Liu, Y. J.; Shors, S.; Smith, R. H.; Chiorini, J.; Kilcoin, N.; Kotin, R. M.; Safer, B.
CORPORATE SOURCE: Molecular Hematol. Branch, Natl. Heart Lung and Blood Inst., Natl. Inst. Health, Bethesda, MD USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 138A.
Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 35 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:555216 BIOSIS
DOCUMENT NUMBER: PREV199699277572
TITLE: Long-term expression of human **factor IX** from mouse hepatocytes after intravenous injection of **AAV** vectors.
AUTHOR(S): Koeberl, D. D. (1); Alexander, I. E.; Miller, A. D.
CORPORATE SOURCE: (1) Univ. Washington, Seattle, WA USA
SOURCE: American Journal of Human Genetics, (1996) Vol. 59, No. 4 SUPPL., pp. A46.
Meeting Info.: 46th Annual Meeting of the American Society of Human Genetics San Francisco, California, USA October 29-November 2, 1996
ISSN: 0002-9297.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 36 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:476541 BIOSIS
DOCUMENT NUMBER: PREV199598490841
TITLE: Transduction of hepatocytes in vivo with **adeno-associated** virus vectors as a model for hepatic gene therapy.
AUTHOR(S): Koeberl, D. D.; Alexander, I. E.; Miller, A. D.
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA USA
SOURCE: American Journal of Human Genetics, (1995) Vol. 57, No. 4 SUPPL., pp. A43.
Meeting Info.: 45th Annual Meeting of the American Society of Human Genetics Minneapolis, Minnesota, USA October 24-28, 1995
ISSN: 0002-9297.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 46 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:250667 CAPLUS
DOCUMENT NUMBER: 128:279551
TITLE: In vitro packaging of **adeno-associated virus** DNA
INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: U.S., 14 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5741683 | A | 19980421 | US 1995-477538 | 19950607 <-- |

AB A method for in vitro packaging of **adeno-assocd** **viral** particles is described. The procedure involves the prepn. of cell-free exts. contg. all the essential components for packaging. Homogeneous purified substrate DNA for packaging may be prepd. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles.

L30 ANSWER 50 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:752722 CAPLUS
DOCUMENT NUMBER: 128:31080
TITLE: In vitro packaging of **adeno-associated virus** DNA
INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5688676 | A | 19971118 | US 1995-477511 | 19950607 <-- |

AB A method for in vitro packaging of **adeno-assocd** **viral** particles is described. The procedure involves the prepn. of cell-free exts. contg. all the essential components for packaging. Homogeneous purified substrate DNA for packaging may be prepd. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles.

L30 ANSWER 51 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:686942 CAPLUS
DOCUMENT NUMBER: 127:327446
TITLE: In vitro packaging of **adeno-associated virus** DNA for therapeutic use without the formation of wild-type **virus**
INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5677158 | A | 19971014 | US 1995-481603 | 19950607 <-- |

AB A method for in vitro packaging of **adeno-assocd** **viral** (**AAV**) particles that avoids the problem of generating wild-type **virus** particles is described. The procedure involves the prepn. of cell-free exts. contg. all the essential components for packaging and a post-packaging treatment to inactivate helper **virus**. The ext. includes a plasmid carrying genes for the **AAV** Rep and VP capsid proteins. Homogeneous purified substrate DNA for packaging may be prepd. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles. In optimization expts. using a genome carrying a lacZ reporter gene, yields of 107 **AAV** particles/mL are reported.

L30 ANSWER 53 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:121369 CAPLUS
DOCUMENT NUMBER: 126:127848
TITLE: In vitro packaging of **adeno-associated virus** DNA for therapeutic use without the formation of wild-type **virus**
INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin,

Sergei; Ni, Tiehua
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9640270 | A1 | 19961219 | WO 1996-US9263 | 19960605 <-- |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| US 5688675 | A | 19971118 | US 1995-476018 | 19950607 <-- |
| CA 2222534 | AA | 19961219 | CA 1996-2222534 | 19960605 <-- |
| AU 9660947 | A1 | 19961230 | AU 1996-60947 | 19960605 <-- |
| AU 706266 | B2 | 19990610 | | |
| EP 836484 | A1 | 19980422 | EP 1996-918243 | 19960605 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 11512923 | T2 | 19991109 | JP 1996-501621 | 19960605 |

PRIORITY APPLN. INFO.: US 1995-476018 19950607
WO 1996-US9263 19960605

AB A method for in vitro packaging of **adeno-assocd**. **viral** (**AAV**) particles that avoids the problem of generating wild-type **virus** particles is described. The procedure involves the prepn. of cell-free exts. contg. all the essential components for packaging and a post-packaging treatment to inactivate helper **virus**. The ext. includes a plasmid carrying genes for the **AAV** Rep and VP proteins. Homogeneous purified substrate DNA for packaging may be prepd. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles. In optimization expts. using a genome carrying a lacZ reporter gene, yields of 107 **AAV** particles/mL are reported.

L30 ANSWER 54 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:428704 CAPLUS
DOCUMENT NUMBER: 125:78521
TITLE: Lipid vesicles containing **adeno-associated** virus rep protein for transgene integration and gene therapy

INVENTOR(S): Wiener, Stephen M.; Chiorini, John A.; Safer, Brian; Kotin, Robert M.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9615777 | A1 | 19960530 | WO 1995-US13190 | 19951116 <-- |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2205874 | AA | 19960530 | CA 1995-2205874 | 19951116 <-- |
| EP 786989 | A1 | 19970806 | EP 1995-943565 | 19951116 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 10509046 | T2 | 19980908 | JP 1995-516836 | 19951116 <-- |

PRIORITY APPLN. INFO.: US 1994-344729 19941123
WO 1995-US13190 19951116

AB A compn. for delivering at least one DNA sequence encoding a desired portion or polypeptide (such as a therapeutic agent) to a cell is claimed. The compn. comprises an **adeno-assocd**. virus rep protein (or a nucleic acid sequence encoding an **adeno-assocd**. virus rep protein) and a genetic construct including at least one DNA sequence encoding a protein or polypeptide or genetic transcript of interest and a promoter controlling the at least one DNA sequence. The genetic construct also includes a first **adeno-assocd**. virus ITR or portion or deriv. thereof and a second **adeno-assocd**. virus ITR or a portion or deriv. thereof. The first and second **adeno-assocd**. virus ITRs or portions or derivs. thereof flank the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest and the promoter controlling the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest. Such a compn. provides for integration of genetic material at a specific locus in the human chromosome, while minimizing the possibility of inadvertent inactivation of host genes and minimizing the possibility of viral contamination. Plasmid pAAVRSVF9, contg. a Rous sarcoma virus promoter fused to the human **factor IX** gene flanked by **adeno-assocd** . virus 5'- and 3'-ITR's, was constructed. Liposomes contg. this plasmid and **adeno-assocd**. virus Rep78 protein were prepd. for use in treatment of hemophilia B.

L30 ANSWER 58 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:951301 CAPLUS
DOCUMENT NUMBER: 123:332111
TITLE: Integrative adenovirus expression vectors for use in gene therapy
INVENTOR(S): Denefle, Patrice; Latta, Martine; Perricaudet, Michel; Vigne, Emmanuelle
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9523867 | A1 | 19950908 | WO 1995-FR233 | 19950228 <-- |
| W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| FR 2716893 | A1 | 19950908 | FR 1994-2445 | 19940303 <-- |
| FR 2716893 | B1 | 19960412 | | |
| CA 2184113 | AA | 19950908 | CA 1995-2184113 | 19950228 <-- |
| AU 9518526 | A1 | 19950918 | AU 1995-18526 | 19950228 <-- |
| EP 748385 | A1 | 19961218 | EP 1995-910605 | 19950228 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| JP 09509578 | T2 | 19970930 | JP 1995-522730 | 19950228 <-- |
| ZA 9501803 | A | 19960109 | ZA 1995-1803 | 19950303 <-- |
| US 6033885 | A | 20000307 | US 1996-702573 | 19960912 |

PRIORITY APPLN. INFO.: FR 1994-2445 19940303
WO 1995-FR233 19950228

AB Recombination-defective adenoviruses carrying a cassette that can be integrated into the genome of host cells are constructed for use in gene therapy. The cassette particularly contains at least one inverted terminal repeat (ITR) of an **adeno-assocd** **virus** (**AAV**) and a therapeutic gene. The use of the **AAV** ITR directs integration to the same locus in all cases and minimizes possible complications from random integration. The construction of **virus** carrying the lacZ reporter gene or a human lipoprotein AI gene under control of **viral** (vesicular stomatitis or Rous sarcoma **virus**) promoters is described.

L30 ANSWER 61 OF 61 CAPLUS COPYRIGHT 2000 ACS
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PATENT ASSIGNEE(S): Chiron Corp., USA
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AB Host cells may be treated for an infection or a hyperproliferative disorder which is characterized by the presence, in the affected cells, of a trans-acting factor capable of regulating gene expression; the therapy involves inserting into the cells a polynucleotide construct having (1) a

cis-acting regulatory sequence which is regulated by the trans-acting factor and (2) an effector gene which renders the cells susceptible to protection or destruction. The cis-acting region may be e.g. homologous to the human immunodeficiency virus (HIV) tar region, and the effector gene may encode ricin A or herpes simplex virus-1 thymidine kinase (HSV-1 tk). On infection with HIV, the HIV tat protein activates the tar region and induces prodn of ricin A, resulting in cell death, or of HSV-1 tk, resulting in cell death with such dideoxynucleotide agents as acyclovir and gancyclovir. Thus, plasmid pTAR1, contg the HIV long terminal repeat (including the tar sequence), a gene encoding chloramphenicol acetyltransferase (CAT), and an SV40 polyadenylation signal and t **intron**, was constructed. Plasmid pTAR1 was transfected into HeLa cells. Plasmid pTAT1, expressing the HIV tat trans-acting agent was transfected into half of the cells. After 48 h, cells were lysed, and lysates were incubated with 14C-labeled chloramphenicol. CAT was expressed in cells contg. both the tar-encoding plasmid and tat-encoding plasmid, but not in cells lacking the pTAT1 plasmid.